BIOGRAPHICAL SKETCH

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NAME: Dolinsky, Joshua L.

eRA COMMONS USER NAME (credential, e.g., agency login): JDOLINSKY

POSITION TITLE: Graduate student researcher

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
UC Santa Barbara	BS	09/2016	06/2020	Biochemistry and Molecular Biology
Brookhaven National Laboratory	N/A	06/2019	07/2019	Nuclear Chemistry
UC Santa Barbara	N/A	09/2020	08/2021	Biomolecular Science and Engineering
UCLA	PhD	09/2021	Expected by 06/2027	Molecular Biology

A. Personal Statement

Understanding protein folding/misfolding and structure has been an interest of mine since undergrad. I started research on tau aggregation in the Lew lab at UC Santa Barbara. There, I learned the basics of protein biochemistry, namely bacterial cloning and column chromatography. During the pandemic, I worked on a mechanobiology project in the Pruitt lab at UC Santa Barbara, through which I learned the basics of AFM and protein patterning. Since starting my PhD at UCLA, I have been involved in two completed structural biology projects. In the first, while rotating in the Yeates lab, I used X-ray crystallography to solve the structure of a bacterial protein that had resisted efforts to be solved for several years. In the second, I performed *in vitro* and cell experiments on D-peptides designed to disaggregate toxic tau fibrils from Alzheimer's Disease patient brains. I was the leading graduate student (i.e., not postdoctoral scholar or project scientist) on that project.

My current project is investigating interactions between the microtubule-binding protein tau and RNA. Tau aggregates into toxic amyloid fibrils in a number of neurodegenerative diseases, most famously Alzheimer's. The Eisenberg lab is a world leader in structural and biochemical characterization of amyloid fibrils. Our lab has led efforts to characterize tau-RNA fibrils structurally, biochemically, and in a cell model. I am in a lab that has excellent resources and a wealth of experienced postdoctoral scholars and project scientists who work collaboratively on projects relating to amyloid fibrils. This environment is the best preparation I could hope for to guide me towards my ultimate goal of becoming a principal investigator in my own right.

1. Miller, J.E., Agdanowski, M.P., **Dolinsky, J.L.,** Sawaya, M.R., Cascio, D., Rodriguez, J.A., Yeates, T.O., 2024. Alphafold-assisted structure determination of a bacterial protein of unknown function using X-ray and electron crystallography. Acta Crystallographica Section D Structural Biology 80, 270–278.
2. Hou, K., Ge, P., Sawaya, M.R., **Dolinsky, J.L.,** Yang, Y., Jiang, Y.X., Lutter, L., Boyer, D.R., Cheng, X., Pi, J., Zhang, J., Lu, J., Yang, S., Yu, Z., Feigon, J., Eisenberg, D.S., 2024. How short peptides can disassemble ultra-stable tau fibrils extracted from Alzheimer's disease brain by a strain-relief mechanism. BioRxiv 586668 [Preprint]. March 25, 2024 [cited September 30, 2024]. Available from: https://doi.org/10.1101/2024.03.25.586668.
3. Hou, K., **Dolinsky, J.L.,** Hu, C.J., Abskharon, R., Zhang, J., Cheng, X., Eisenberg, D.S. 2023, March 19-22. Structure-based design of D-peptide Inhibitors of Tau Aggregation in Alzheimer's Disease. West Coast Structural Biology Workshop, Monterey, CA, USA.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 – present Graduate mentor, PhD and Undergraduate Life Scientists in Academic Research, UCLA
2021 – present Graduate Student Researcher in Molecular Biology, UCLA
2020 – 2021 Research Assistant in Biomedical Science and Engineering, UC Santa Barbara
2019 – 2020 Undergraduate Researcher in Biochemistry and Molecular Biology, UC Santa Barbara

Honors and Awards

2023 Poster presenter, West Coast Structural Biology Workshop
2020 Graduated with high honors, UC Santa Barbara College of Letters and Science
2020 Academic Excellence Award, UC Santa Barbara College of Letters and Science Honors Program
2020 Distinction in the major, UC Santa Barbara Molecular, Cellular, and Developmental Biology Department
2016 – 2020 Regents Scholar, UC Santa Barbara

C. Contributions to Science

1. Solving the structures of previously unsolvable proteins with X-ray crystallography

In the lab of Professor Jose Rodriguez at UCLA, I used AlphaFold to predict the structure of a yeast protein in the so-called dark proteome of unstudied, small proteins. After editing AlphaFold's models, I was able to determine the phases for an X-ray crystallography dataset that had previously proved resistant to structure determination. In the lab of Professor Todd Yeates at UCLA, I determined the structure of crystals of a yeast protein that had been difficult to solve by X-ray diffraction. I grew protein crystals that were shot on a microfocus X-ray synchrotron beamline. Because the crystals were thin and got damaged quickly, I had to combine partial datasets from multiple crystals. This data, combined with microED data collected by a labmate, showed that the protein preferentially formed crystals when its second domain, which was mostly unstructured, was autocatalytically cleaved off.

1. Miller, J.E., Agdanowski, M.P., **Dolinsky, J.L.,** Sawaya, M.R., Cascio, D., Rodriguez, J.A., Yeates, T.O., 2024. Alphafold-assisted structure determination of a bacterial protein of unknown function using X-ray and electron crystallography. Acta Crystallographica Section D Structural Biology 80, 270–278

2. Structure-based design of D-peptides that fragment amyloid fibrils

I joined the lab of Professor David Eisenberg at UCLA. My first project was testing D-peptides that our lab had designed rationally against tau fibrils from Alzheimer's Disease based on fibril structure. These peptides, which had sequence D-TLKVIWX, inhibited further fibril aggregation, and as it turned out, also disassembled the tau fibrils. I tested roughly a dozen of these D-peptides *in vitro* and in cell models to determine their efficacy in amyloid fibril aggregation inhibition and amyloid fibril disassembly, their ability to seed tau fibrillization in cells, and their impact on cell viability. D-peptides with a nonpolar seventh residue performed the best across all tested metrics. I also showed that the these peptides needed to form inter-peptide hydrogen bonds to fibrillize and have maximal efficacy. Ultimately, one of these peptides was tested in an Alzheimer's mouse model and partially rescued cognitive deficits. Our lab proposed a strain-relief mechanism of tau fibril disassembly via D-peptides that could be generalizable to other amyloid fibrils.

1. Hou, K., Ge, P., Sawaya, M.R., **Dolinsky, J.L.,** Yang, Y., Jiang, Y.X., Lutter, L., Boyer, D.R., Cheng, X., Pi, J., Zhang, J., Lu, J., Yang, S., Yu, Z., Feigon, J., Eisenberg, D.S., 2024. How short peptides can disassemble ultra-stable tau fibrils extracted from Alzheimer's disease brain by a strain-relief mechanism. BioRxiv 586668 [Preprint]. March 25, 2024 [cited September 30, 2024]. Available from: https://doi.org/10.1101/2024.03.25.586668.
    a. This preprint was discussed in the 4/19/24 AlzForum weekly newsletter: https://www.alzforum.org/news/research-news/tau-toggling-peptides-one-seeds-fibrils-other-dismantles-them
2. 2. Hou K., Pan H, Shahpasand-Kroner, H., Hu, C.J., Abskharon, R., Seidler, P., Mekkittikul, M., Balbirnie, M., Lantz, C., Sawaya, M.R., **Dolinsky, J.L**., Jones, M., Zuo, X., Loo, J.A., Frautschy,

S., Cole, G., Eisenberg, D.S., 2024. D-peptide-magnetic nanoparticles fragment tau fibrils and rescue behavioral deficits in a mouse model of Alzheimer's disease. Sci Adv. 2024;10(18):eadl2991.

3. Hou, K., **Dolinsky, J.L.,** Hu, C.J., Abskharon, R., Zhang, J., Cheng, X., Eisenberg, D.S. 2023, March 19-22. Structure-based design of D-peptide Inhibitors of Tau Aggregation in Alzheimer's Disease. West Coast Structural Biology Workshop, Monterey, CA, USA.

D. Scholastic Performance

YEAR	COURSE TITLE	GRADE
	UC Santa Barbara: Undergraduate Classes	
2016	Introduction to Biological Anthropology	A+
2016	General Chemistry A	A+
2016	General Chemistry Lab A	A
2016	Introduction to University Research	P
2016	Biology Mentoring and Engagement I	P
2016	Introduction to Psychology	A
2017	General Chemistry B	A
2017	General Chemistry Lab B	A
2017	Principles of Microeconomics	A
2017	The Case Against Science	P
2017	Biology Mentoring and Engagement II	P
2017	Introductory Experimental Physics A	B
2017	Introductory Experimental Physics Lab A	A
2017	General Chemistry C	B
2017	General Chemistry Lab C	B+
2017	The Elegant Universe	P
2017	Linear Algebra with Applications	A
2017	Biology Mentoring and Engagement III	P
2017	Introductory Experimental Physics B	B+
2017	Introductory Experimental Physics Lab B	B+
2017	Honors Organic Chemistry A	A
2017	Introductory Biology Lab I	B
2017	Introductory Biology I	A+
2017	Introduction to Ethics	A+
2017	Probability and Statistics	C
2018	Honors Organic Chemistry B	A
2018	Introductory Biology II: Ecology and Evolution	A
2018	Transfer Exploration Seminar	P
2018	Introductory Biology II: Physiology	A+
2018	Introductory Biology Lab II	A+
2018	Honors Organic Chemistry C	A-
2018	Principles of Macroeconomics	A
2018	Introductory Biology III	A+
2018	Introductory Biology Lab III	B-
2018	Global History, Culture, and Ideology	A+
2018	Science Fiction Literature	A
2018	Music Appreciation	A

YEAR	COURSE TITLE	GRADE
2018	Introductory Experimental Physics C	A
2018	Introductory Experimental Physics Lab C	A+
2018	Writing and Public Discourse	W
2018	Art Survey I: Ancient-Medieval Art	A
2018	Laboratory Methods in Organic Chemistry A	B
2018	Intermediate Microeconomic Theory	A-
2018	Introduction to Teaching in Biology	P
2018	Biochemistry - Structure and Function of Macromolecules	A+
2019	Laboratory Methods in Organic Chemistry B	A
2019	Biochemistry – Bioenergetics, Enzymology, and Metabolism	A-
2019	Introduction to Teaching in Biology	P
2019	Molecular Genetics I: Prokaryotes	A
2019	Molecular Genetics I: Prokaryotes - Honors	A
2019	Cytokine Action and Viral Pathogenesis	A
2019	Vector Calculus With Applications I	B-
2019	Molecular Genetics II: Eukaryotes	A
2019	Biochemistry – Computational and Systems Biology	A
2019	General Animal Virology	A+
2019	Molecular, Cell, and Developmental Biology Independent Studies	P
2019	Introduction to US Minority Literature	A+
2019	Human Physiology	B+
2019	Molecular, Cell, and Developmental Biology Independent Studies	P
2019	Physical Chemistry: Chemical Thermodynamics	A
2019	Analytical Chemistry	A+
2019	Honors Seminar: Sansum Clinic Shadowing Program	A
2019	Cell Biology	A
2019	Molecular, Cell, and Developmental Biology Independent Studies	P
2020	Structure and Reactivity in Organic Chemistry	A
2020	Underserved Medicine	P
2020	Experimental Strategies in Physical Biochemistry	A
2020	Molecular, Cell, and Developmental Biology Independent Studies	P
2020	Introduction to Sociology	A
2020	Astrobiology and the Origins of Life	A
2020	Molecular, Cell, and Developmental Biology Independent Studies	P
2020	Laboratory in Biochemistry	A
2020	Cellular Growth Control and Oncogenesis	A
2020	Cellular Growth Control and Oncogenesis - Honors	A
2020	Writing for Health Professions	A
	Stony Brook University/Brookhaven National Lab: Undergraduate Classes	
2019	Nuclear Chemistry	A
2019	Nuclear Chemistry Laboratory	A
	UC Santa Barbara: Graduate Classes	
2020	Methods in Mechanobiology and Biofabrication	A
2020	Biomolecular Materials II: Applications	A+
2020	Protein Structure and Function	A+

YEAR	COURSE TITLE	GRADE
2020	Biomolecular Science and Engineering Discussion Group	S
2020	Bioengineering: Career and Development Opportunites	S
2020	Biomolecular Science and Engineering Directed Reading and Research	A
2020	Teaching Assistant Orientation	S
2020	Techniques of Teaching and Laboratory Class Supervision	S
2021	Colloids and Interfaces I	A+
2021	Biomolecular Science and Engineering Discussion Group	S
2021	Biomolecular Science and Engineering Directed Reading and Research	A
2021	Practicum in Instruction	S
2021	Biophysical Thermodynamics	A
2021	Colloids and Interfaces II	A
2021	Biomolecular Science and Engineering Directed Reading and Research	A
2021	Biomolecular Science and Engineering Discussion Group	S
	UCLA: Graduate Classes	
2021	Concepts in Molecular Biosciences: Structural Biology	B+
2021	Concepts in Molecular Biosciences: Cell Biological Mechanisms of Neurodegenerative Disease	B+
2021	Molecular Biology Directed Individual Studies	S
2022	Structural Molecular Biology	A-
2022	Structural Molecular Biology Laboratory	A
2022	Scientific Writing	A
2022	Molecular Biology Directed Individual Studies	S
2022	Proteomics and Protein Mass Spectrometry	A
2022	Ethics and Accountability in Biomedical Research	S
2023	Preparation for College-Level Teaching in Life Sciences	S
2022-present	Molecular Biology Directed Individual Studies (every quarter)	S

Some UC Santa Barbara undergraduate classes are graded as pass/no pass (P/NP), and a pass grade indicates a grade of C or higher. These classes tend to be 1-2 units and not directly relevant to a given major, for instance interdisciplinary seminar classes. For the Writing and Public Discourse class I took in 2018, I was granted permission to withdraw from it after the deadline to drop courses. At both UC Santa Barbara and UCLA, some classes are graded as satisfactory/not satisfactory (S/NS), and a satisfactory grade indicates a grade of B or higher. None of P/NP, S/NS, or W grades impact GPA.

BIOGRAPHICAL SKETCH

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NAME: Peng Ge

eRA COMMONS USER NAME (credential, e.g., agency login): gepeng22

POSITION TITLE: Research Specialist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Peking University, Beijing, P.R. China	B.S.	07/01	Chemistry
(matriculated at the age of 14)			
Baylor College of Medicine, Houston, TX	Ph.D.	09/10	Structural Computational Biology and Molecular Biophysics
UCLA, Los Angeles, CA	Post Doc	03/16	Structural Biology

A. Personal Statement

I started my professional training as a structural, organic chemist and a drug designer at Peking University, China. In 2003, I came to the U.S. for my graduate study, first at Rice University in Houston, TX in the area of applied physics and then drifted across the Main Street to Baylor College of Medicine and studied structural biology under the mentorship of several cryoEM structural biologists at the Texas Medical Center. In my 17 years of professional research career, I published a total of 28 papers including 6 articles in top tier journals (3 first author articles) and 15 articles in second tier journals (6 first author articles).

I am well experienced as a structural biologist specializing in cryo-electron microscopy, as exemplified by my publication record below in the fields of amyloid fibrils, bacterial contractile nano-machines, cryo-EM method development and RNA viruses.

B. Positions, Scientific Appointments, and Honors

Professional Experience

2001-2003	Research Assistant, the State Key Laboratory for Structural Chemistry of Unstable and Stable Species, Beijing, China, P.R., supervised by Dr. Luhua Lai
2003-2004	Ph. D. Student, Applied Physics Program, Rice University, Houston, TX 77025
2004-2010	Ph. D. Student, Program in Structure and Computational Biology and Molecular Biophysics, Baylor College of Medicine, Houston, TX 77030
2010-2106	Postdoctoral Scholar, Department of Microbiology, Immunology and Molecular Genetics, UCLA, Los Angeles, CA 90095
2016-2021	Researcher, California Nanosystem Institute, UCLA, Los Angeles, CA 90095
2021-2023	Research Specialist, HHMI, UCLA, Los Angeles, CA 90095
2024-present	Research Scientist, UCLA, Los Angeles, CA 90095

Honors

2003	Dean's Fellowship, Department of Bioengineering, Rice University, Houston, TX
2006	Keck Viral Imaging Fellowship, Houston, TX
2013	George Palade Award, Microscopy Society of America
2013-15	American Heart Association Western Affiliates Postdoctoral Fellowship
2014	Boyer-Peter Award, Molecular Biology Institute, UCLA, Los Angeles, CA
2015	Chancellor's Award for Postdoctoral Research, UCLA, Los Angeles, CA
2015	Sydney Finegold Award, MIMG Dept, UCLA, Los Angeles, CA

C. Contributions to Science

1. Methodology development for atomic resolution cryoEM.

Very recently, the structural biology method of cryo electron microscopy (cryoEM) has gained public attention as a new way of understanding biological systems. I contributed to the development of cryoEM methods. Publication #d here is the first helical cryoEM structure to reach near atomic resolution. This method is further extended to incorporate the Relion framework that uses maximum-likelihood estimations (#c) and is applied to systems previously too flexible or too fine to study by cryoEM (#a,b).

a. Guenther EL, **Ge P**, Trinh H, Sawaya MR, Cascio D, Boyer DR, Gonen T, Zhou ZH, Eisenberg DS. Atomic-level evidence for packing and positional amyloid polymorphism by segment from TDP-43 RRM2. **Nat Struct Mol Biol.** 25 (2018) 311 PMC6056015

b. Poweleit N, **Ge P**, Nguyen HH, Loo RR, Gunsalus RP, Zhou ZH. CryoEM structure of the Methanospirillum hungatei archaellum reveals structural features distinct from the bacterial flagellum and type IV pilus. **Nat Microbiol**. 2 (2016) 16222 PMC5695567

c. Clemens DL**, **Ge P****, Lee B-Y, Horwitz MA and Zhou ZH Atomic structure and mutagenesis of a type VI secretion system reveals a mesh framework essential to function. **Cell**, 160 (2015) 940-51 PMC4351867 ****Co-First Authors**

d. **Ge P**, Zhou ZH Hydrogen-bonding networks and RNA bases revealed by cryo electron microscopy suggest a triggering mechanism for calcium switches. **Proc Natl Acad Sci USA** 109 (2011) 9637-42 PMC3111329

2. Structural study of Amyloid fibers

Amyloid fibers are central to many neural degenerative diseases such as Frontotemporal lobar degeneration (FTLD, #a-c), mad cow, Alzheimer and Parkinson (#d) diseases. The structural study of these fibers by cryoEM was difficult due to the fine helical parameters. The advent of a direct electron detecting camera provided the required high-resolution contrast at low dose, making possible the determination of many such filaments.

a. Hou K, **Ge P**, Sawaya MR,… Eisenberg DS. How short peptides can disassemble ultra-stable tau fibrils extracted from Alzheimer's disease brain by a strain-relief mechanism. **bioRxiv**. (2024) Preprint

b. Jiang YX, Cao Q, Sawaya MR, Abskharon R, **Ge P**, …, Eisenberg DS. Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP-43. **Nature**. 605(2022) 304 PMC9844993

c. Cao Q, Boyer DR, Sawaya MR, **Ge P**, Eisenberg DS. Cryo-EM structures of four polymorphic TDP-43 amyloid cores. **Nat Struct Mol Biol.** 26 (2019) 619 PMC7047951

d. Li B**, **Ge P****, Murray KA**, et al. Cryo-EM of full-length α-synuclein reveals fibril polymorphs with a common structural kernel. **Nat Commun.** 9 (2018) 3609 ****Co-First Authors** PMC6127345 (highly cited article)

3. Structure-function relationship of bacterial contractile nanomachines.

Contractile nanomachines are a collection of bacterial protein assemblies, either intracellular or extracellular, that drive their central tubes into victim cells by force generated with sheath contraction. The atomic resolution structures of these systems provide basis for redesign of such machines (#a,b) and for development of therapeutic agents against such machines (#c).

a. **Ge P****, Scholl D**, Prokhorov NS, Avaylon J, Shneider MM, Browning C, Buth SA, Plattner M, Chakraborty U, Ding K, Leiman PG, Miller JF, Zhou ZH. Action of a minimal contractile bactericidal nanomachine **Nature** 580 (2020) 658-62 PMC7513463 ****Co-First Authors**

b. **Ge P**, Scholl D, Leiman PG, Yu X, Miller JF, Zhou ZH Atomic structures of a bactericidal contractile nanotube in its pre- and post-contraction states. **Nat Struct Mol Biol,** 22 (2015) 377-82 PMC4445970

c. Clemens DL**, **Ge P****, Lee B-Y, Horwitz MA and Zhou ZH Atomic structure and mutagenesis of a type VI secretion system reveals a mesh framework essential to function. **Cell**, 160 (2015) 940-51 PMC4351867 ****Co-First Authors**

4. Structural study of RNA viruses

Many human pathogens contain RNA as their genetic material. These include viruses under the families of non-segmented negative-strand RNA viruses (rabies virus, vesicular stomatitis virus and ebola virus, #d), flaviviruses (dengue virus, #b,c) and double strand RNA viruses (bluetongue virus, #a). Atomic structure of these viruses are desirable for the purpose of structure-based drug discovery against these viruses.

d. Kerviel A**, Ge P**, Lai M**, Jih J, Boyce M, Zhang X, Zhou ZH, Roy P. Atomic structure of the translation regulatory protein NS1 of bluetongue virus. Nat Microbiol. 4 (2019) 837-845 PMC6482088 ****Co-First Authors**

a. **Ge P**, Zhou ZH Class II viral fusion proteins: chaperone, maturation and entropy. **Trends Microbiol.** 22 (2014) 100-106. PMC4445943

b. Zhang X****, **Ge P****, Yu X, Brannan JM, Bi G, Zhang Q, Schein S, Zhou ZH. Cryo-EM structure of the mature dengue virus at 3.5-Å resolution. **Nat Struct Mol Biol.** 20 (2013) 105-110. ****Co-First Authors** (Journal Cover) PMC3593067 (highly cited article)

c. **Ge P**, Tsao J, Schein S, Green TJ, Luo M, Zhou ZH. Cryo-EM model of the bullet-shaped vesicular stomatitis virus. **Science** 327 (2010) 689-93. PMC2892700

5. Structural study of single particle protein complexes

a. Jiang J, Magilnick N, Tsirulnikov K, Abuladze N, Atanasov I, **Ge P**, Narla M, Pushkin A, Zhou ZH, Kurtz I. Single particle electron microscopy analysis of the bovine anion exchanger 1 reveals a flexible linker connecting the cytoplasmic and membrane domains. **Plos One**. 8 (2013) e55408. PMC3564912

b. Huang CS, **Ge P**, Zhou ZH, Tong L An unanticipated architecture of the 750-kDa $\alpha_6\beta_6$ holoenzyme of 3-methylcrotonyl-CoA carboxylase. **Nature** 481 (2012) 219-223. PMC3271731

c. Green TJ, Rowse M, Tsao J, Kang J, **Ge P**, Zhou ZH and Luo M Access of RNA encapsidated in the nucleocapsid of vesicular stomatitis virus, **J. Virol.** 85 (2011) 2714-2722. PMC3067934

d. Li F, **Ge P**, Hui WH, Atanasov I, Rogers K, Guo Q, Osato D, Falick AM, Zhou ZH, Simpson L Structure of the core editing complex (L-complex) involved in uridine insertion/deletion RNA editing in trypanosomatid mitochondria. **Proc Natl Acad Sci USA** 106 (2009) 12306-10 PMC2708173

Complete List of Published Work:
https://www.ncbi.nlm.nih.gov/myncbi/peng.ge.1/bibliography/public/

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Dr. David Eisenberg

eRA COMMONS USER NAME (credential, e.g., agency login): eisenberg2

POSITION TITLE: Professor of Molecular Biology; Paul D. Boyer Chair of Molecular Biology, UCLA

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard College	B.A.	1961	Biochemical Sciences
Oxford College	D. Phil	1964	Theoretical Chemistry
Princeton University	NSF Postdoctoral Fellow	1966	Biophysical Chemistry

A. Personal Statement

Understanding biology and disease has been my career-long interest. Starting with biochemistry, computation and structural methods, I have focused increasingly on proteins associated with amyloid and prion diseases. These are diseases of protein oligomerization and fibrillation. By newly developed methods of microcrystallography, cryo-EM, and microelectron diffraction, our lab has been able to determine the atomic structures of some 225 disease related fibril structures. In the past 5 years, we have determined structures of two dozen amyloid fibrils by cryoEM. Since 2022 we have used structure-based methods to discover small molecules and peptides capable of disassembly of pathogenic amyloid fibrils associated with Alzheimer's and Parkinson's diseases.

In laboratory training, I have supervised dozens of undergraduates, some 150 Ph.D. theses and postdoctoral fellows, most of who are carrying out research in structural and computational biology in universities, research institutes, and industries. Former lab members work in at least a dozen countries. I have coauthored ~400 research papers and reviews, and two books: a monograph on the structure and properties of water [>6000 citations], a text on physical chemistry for the life sciences. I established a user-friendly facility for determination of atomic structures by x-ray and EM methods which has welcomed and helped scores of users from UCLA, other research institutions and industry.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2009-Present Paul D. Boyer Chair, UCLA
1976-Present Professor of Molecular Biology, UCLA
2001-2023 HHMI Investigator, Howard Hughes Medical Institute

1993-2014 Director, UCLA-DOE Institute for Genomics and Proteomics
1971-1976 Associate Professor of Molecular Biology, UCLA
1968-1971 Assistant Professor of Molecular Biology, UCLA
1966-1969 Research Fellow in Structural Chemistry, Caltech

Selected awards

2020 Passano Laureate
2008 Preceptor, Nobel Laureate Signature Award for Graduate Education in Chemistry
2003 Member American Philosophical Society
2002 National Academy of Medicine
1991 Fellow, American Academy of Arts and Sciences
1989 Member, National Academy of Sciences
1975 UCLA Distinguished Teaching Award
1961-1964 Rhodes Scholarship
1961 Best undergraduate thesis in Biochemical Sciences

C. Contributions to Science [Google Scholar citations n = 123,000; h=158]

1. **Structural biology of the amyloid state of proteins.** Paper a was the first atomic resolution structure of the amyloid state. Paper b showed that numerous amyloid fibrils have steric-zipper spines, and classified the possible symmetries of this structural motif. Paper c reports reveals a new type of protein interaction—termed LARKS—between low-complexity domains, responsible for multivalent networks and gels, such as those found in membrane-less organelles. Paper d reports the unexpected discovery that amyloid fibrils in some post mortem brains of patients clinically and pathologically certified as FTLD-TDP have amyloid fibrils of the C-terminal domain of a lysosomal protein TMEM106B, rather than the expected TDP-43.

a. Nelson R, Sawaya MR, Balbirnie M, Madsen AO, Riekel C, Grothe R, Eisenberg D. Structure of the cross-beta spine of amyloid-like fibrils. Nature. **435**, 773-8 (2005). PMCID: PMC1479801 [2600 citations]

b. Sawaya MR, Sambashivan S, Nelson R, Ivanova MI, Sievers SA, Apostol MI, Thompson MJ, Balbirnie M, Wiltzius JJ, McFarlane HT, Madsen AØ, Riekel C, Eisenberg D. Atomic structures of amyloid cross-beta spines reveal varied steric zippers. *Nature*. **447**, 453-7 (2007). PMID: 17468747 [2500 citations]

c. Michael P. Hughes, Michael R. Sawaya, David R. Boyer, Lukasz Goldschmidt, Jose A. Rodriguez, Duilio Cascio, Lisa Chong, Tamir Gonen, David S. Eisenberg. Atomic structures of low-complexity protein segments reveal kinked β-sheets that assemble into networks. *Science*. **359**, 698-701 (2018). PMCID: PMC6192703

d. Yi Xiao Jiang, Qin Cao, Michael R. Sawaya, Romany Abskharon, Peng Ge, Michael DeTure, Dennis W. Dickson4, Janine Y. Fu, Rachel R. Ogorzalek Loo, Joseph A. Loo, David S. Eisenberg. Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP-43. *Nature*, **605**, 304 (2022).

2. **Inhibition of formation cytotoxicity of amyloid fibrils and fibril disassemblers:** Dozens of human diseases are associated with amyloid fibrils. We have been able to inhibit amyloid formation and to disassemble brain-derived fibrils by structure-based design (papers e-h). Papers g and h report improved inhibitors and disassemblers of tau fibrils (at the root of Alzheimer's, CTE, and dozens of other tauopathies.

e. Sievers SA, Karanicolas J, Chang HW, Zhao A, Jiang L, Zirafi O, Stevens JT, Munch J, Baker D, Eisenberg D. Structure-based design of non-natural amino-acid inhibitors of amyloid fibril formation. *Nature*. **475**, 96-100 (2011). PMCID: PMC4073670 [461 citations]

f. Seidler PM, Boyer DR, Murray KA, Yang TP, Bentzel M, Sawaya MR, Rosenberg G, Cascio D, Williams CK, Newell K, Ghetti B, DeTure MA, Dickson D, Vinters HV, Eisenberg DS* Structure-based inhibitors halt prion-like seeding by Alzheimer's disease– and tauopathy-derived brain tissue samples *J Biol Chem*, **294**: 16451-16464, Nov 1 (2019)

g. Paul M. Seidler, Kevin A. Murray, David R. Boyer , Peng Ge , Michael R. Sawaya, Carolyn J. Hu, Xinyi Cheng, Romany Abskharon, Michael A. DeTure, Christopher K. Williams, Dennis W. Dickson, Harry V. Vinters, & David S. Eisenberg. Structure-based discovery of small molecules that disaggregate Alzheimer's disease tissue derived tau fibrils in vitro, *Nature Comms*. (2022)

h. “Small molecules disaggregate alpha-synuclein and prevent seeding from patient brain-derived fibrils”, Kevin A. Murray, Carolyn J. Hu, Hope Pana,, Jiahui Lua,, Romany Abskharona, Jeannette T. Bowler, Gregory M. Rosenberg, Christopher K. Williamsc, Gazmend Elezid, Melinda Balbirniea,, Kym F. Faull, Harry V. Vinters, Paul M. Seidler, and David S. Eisenberg, *PNAS* **120** (7) e2217835120.

3. **Computational analysis of amino acid sequences and protein structures:** As protein sequences and structures became readily available in the 1980s and 1990s, I developed new methods to extract information from sequences and structures. Paper i describes a new property of proteins—the hydrophobic moment, which has been widely applied to detect periodicities in proteins. Paper j introduced atomic solvation parameters, used subsequently by many to estimate free energy changes of protein folding and binding. Paper k introduced the Profile method for detection of distantly related protein sequences. It was later coded by others into the powerful PsiBlast algorithm. Paper l invented threading of sequences on to structures to identify new proteins having previously determined folds. This method has also been widely applied.

i. D Eisenberg, RM Weiss, TC Terwilliger. The hydrophobic moment detects periodicity in protein hydrophobicity. *Proc. Natl. Acad. Sci. U.S.A.* **81**, 140-144 (1984). PMCID: PMC344626 [1200 citations]

j. D. Eisenberg, A.D. McLachlan. Solvation energy in protein folding and binding. Nature. 319,199-203 (1986). PMID: 3945310 [2400 citations]

k. M Gribskov, AD McLachlan, D Eisenberg. Profile analysis: detection of distantly related proteins. Proc. Natl. Acad. Sci. U.S.A. **84**, 4355-4358 (1987). PMCID: PMC305087 [1800 citations]

l. JU Bowie, R Luthy, D Eisenberg. A method to identify protein sequences that fold into a known 3D structure. *Science*. **253**, 164-170 (1991). PMID: 1853201 [3600 citations]

4. **Methods for inferring protein interactions and functions from genome sequences.** The advent of genome sequencing brought the puzzle of how to infer from this mass of information the function of proteins and the pathways and complexes formed by proteins. Our group, together with the group of Todd Yeates, worked out several methods described in papers m, n, and o. We began a web-accessible database of protein interactions (paper o), and a web-accessible Amyloid Atlas (paper p).

m. Marcotte EM, Pellegrini M, Ng HL, Rice DW, Yeates TO, Eisenberg D. Detecting protein function and protein-protein interactions from genome sequences. *Science.* **285, 751-3** (1999). PMID: 10427000 [2200 citations]

n. Marcotte EM, Pellegrini M, Thompson MJ, Yeates TO, Eisenberg D. A combined algorithm for genome-wide prediction of protein function. *Nature*. **402**, 83-6 (1999). PMID: 10573421 [1200 citations]

o. Xenarios I, Salwínski L, Duan XJ, Higney P, Kim SM, Eisenberg D. DIP, the Database of Interacting Proteins: a research tool for studying cellular networks of protein interactions. *Nucleic Acids Res.* **30**, 303-5 (2100). PMCID: PMC99070 [2038 citations]

p. Sawaya MR, Hughes MP, Rodriguez JA, Riek R, Eisenberg DS The expanding amyloid family: Structure, stability, function, and pathogenesis. Cell. Sep 2021. 184(19):4857-4873. 2021 PMID: 34534463

Selected scientific discoveries

a. First EM-based 3D reconstruction from EM data [J. Frank, Eisenberg et al. Ultramicroscopy, 1978]
b. The hydrophobic moment [Eisenberg et al. Nature, 1982]
c. Solvation energy in protein folding and binding [Eisenberg & McLachlan, Nature 1986]
d. Profile analysis: Detection of distantly related proteins [Gribskov, McLachlan, Eisenberg, PNAS, 1987]
e. Method to identity protein sequences that fold into a known 3D structure, [Bowie et al. Science, 1991]
f. Assessment of protein models with 3D profiles [Luthy, Bowie, & Eisenberg, Nature,1992]
g. Protein domain swapping [Bennett et al., PNAS 1994]
h. Detection of protein function from genome sequences [Marcotte et al., Science, 1999]
i. First atomic structure of an amyloid fibril [Nelson et al., Nature, 2005]
j. First designed inhibitors of amyloid fibrils [Sievers et al. Nature, 2011]
k. First protein (peptide) structure by electron diffraction [Rodriguez et al. Nature, 2015]
l. First structure-based discovery of small molecules that disassemble pathogenic tau fibrils from Alzheimer’s brains [Seidler et al. Nature Comms, 2022]

Selected scientific public service

Editor, Advances in Protein Chemistry 1989- 2009
NIH Sudy Sections 1972. 1973-1977. 1980, 1982,1983, 2012, 2014, 2020
Organizing Committee, The Protein Society, 1985-87
First elected president, The Protein Society, 1987-89
Advisory Board, Protein Data Bank, 1995-1999, Chair, 1996-1997
Organizing Chair, National Academy of Sciences Biophysics Section, 2001 – 2004
Advisory Committee, Swiss National Science Foundation Center of Excellence in Structural Biology, 2002-2007
ADRx, Inc., Co-founder and Chair, Scientific Advisory Board, 2014-

Current laboratory support

1RF1AG065407 (Rakez Kayed, U. Texas) 07/01/2021 – 06/31/2026 1.50 calendar months NIH $939,220 Total
Interdisciplinary Research Network on Biologically Active Tau Aggregate Polymorphs from Alzheimer's Disease and Related Dementias
The Eisenberg lab will prepare oligomeric specimens for structural studies, including cryo-EM. Antibodies and nanobodies will be prepared for aids in specimen preparation. Cryo-EM and crystallographic structural determinations will be carried out.

1R01AG070895 (Eisenberg) 02/01/22 – 01/31/27 4.00 calendar months
NIH $1,068,649 Total
Towards Treatment of Alzheimer's Disease by Targeting Pathogenic Tau and Beta-Amyloid Structures
To develop effective drugs, we take the approach that has been effective for treating cancer and HIV-AIDS: structure-based drug design by applying the powerful tools of electron microscopy and x-ray diffraction.

Recently expired and currently expiring laboratory support

HHMI (Eisenberg) 09/01/18 – 08/31/23 0 calendar months
Howard Hughes Medical Institute
General Support of the Eisenberg laboratory, including salaries for PI (Eisenberg), Crystallographer, and Laboratory Manager, and Administrative Assistant.

R01 AG048120 (Eisenberg) 06/01/2019 – 05/31/2024 1.50 calendar months
NIH/NIA $1,950,000 Total
Development of Inhibitors and Diagnostics for Systemic Amyloid Diseases
We aim to further our understanding of amyloid structure, and apply this understanding to the development of new and better candidate therapeutics and diagnostics.

RF1AG065407 (Marc Diamond PI) 09/15/2020 – 08/31/2024 0.50 calendar months
NIH $303,145 Total
Seeds and Strains Derived from Tau Monomer
We will oversee the characterization of tauopathy-derived brain fibrils using cryo-electron microscopy (cryoEM). His group will create micro-crystals of subdomains (i.e. local structures) of the tau protein for x-ray crystallography. This will be used to test predictions made by cross-linking mass spectrometry and other biophysical studies performed in the Joachimiak lab.